REMARKS

A check for $510 for the fee for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. Supporting documents accompany this response and are provided for the Examiner's convenience.

Claims 50-52, 54-59 and 61-65 are currently pending. Claims 53 and 60 are cancelled herein without prejudice or disclaimer. Claims 50-52, 55 and 56 are amended herein. Claims 62-65 are added herein. Claim 50 is amended to include the limitations of claims 53 and 60, which are cancelled herein (and see page 19, lines 1-5 and 9-12). Claim 50 also is amended to more distinctly claim the subject matter by reciting that the device is adapted for long-term release of the agent. Basis for the amendment is found throughout the specification (*e.g.*, see page 26, lines 3-12). Claim 50 also is amended to recite that the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent. Basis for the amendment is found throughout the specification (*e.g.*, see page 5, lines 4-6). Claim 52 is amended to correct dependency and formatting. Claims 55 and 56 are amended to correct a typographical error. Basis for the amendment is found throughout the specification (*e.g.*, see claims 55 and 56 as originally filed). Basis for new claim 62 is found throughout the specification ((*e.g.*, see page 26, lines 1-2). Basis for new claim 63 is found throughout the specification (*e.g.*, see page 19, lines 9-12 and page 26, lines 3-19). Basis for new claim 64 is found throughout the specification (*e.g.*, see original claim 57). Basis for new claim 65 is found throughout the specification (*e.g.*, see page 5, line 1). No new matter is added.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 50 and 53-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3, 5-7 and 13-15 of copending U.S. Patent Appln. No. 11/127,544. The Examiner alleges that, although the conflicting claims are not identical, they are not patently distinct, because "while the copending claims do not recite the length of time for which the composition must effect release of the drug, it would be obvious to the artisan to deliver the drug for a length of time appropriate to treat the condition of interest, and the artisan would be able to judge what this length of time is."

The rejection is respectfully traversed. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

RELEVANT LAW

Obviousness-type double patenting occurs when that the difference between a first-patented invention and its variant involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. See, *e.g.*, *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 23 USPQ2d 1839, 1845 (Fed. Cir. 1992). Analysis of obvious-type double patenting involves a comparison of the subject invention "with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." *Id.* (emphasis in original); *see, also, Ortho Pharm. Corp. v. Smith*, 22 USPQ2d 1119, 1125 (Fed. Cir. 1992) ("It is the claims, not the specification that defines an invention [citation] . . . [a]nd it is the claims that are compared when assessing double patenting."). Thus, an obviousness-type double patenting rejection is based on the claims and not on the disclosure of a patent.

The comparison between claims in an obviousness-type double patenting inquiry requires the use of a fundamental rule of claim construction, that the invention is defined by the claim taken as a whole -- every claim limitation (or each step) being material to the description of the invention. *Ortho Pharm. Corp.*, 22 USPQ2d at 1125. Thus, it is inappropriate to base a double patenting rejection on the disclosure of a patent, even when such disclosure is found in the claims.

Obviousness-type double-patenting has not been found when the claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue. See, *e.g.*, *Id.*

Obviousness-type double-patenting only is applicable to a later issuing application and is only based upon the claims in the two cases. Furthermore, if the order of issuance results from delays in the Patent Office, not from actions of the applicant, then a two-way distinctness test must be applied. See, *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991) in which the CAFC held that in certain circumstances, a third inquiry to support an obviousness-type double rejection will only be sustained if the application claims are not patentably distinct from the prior patent claims and the prior patent claims are also not patentably distinct from the applications claims.

ANALYSIS

It is first noted that issues of obviousness-type double patenting cannot be resolved until one case has issued and there are allowable claims in the other case or at least until there are allowable claims in both applications.

U.S. application Serial No. 11/127,544

It respectfully is submitted that, as between the presently pending claims of copending U.S. application Serial No. 11/127,544 and the claims in the instant application, obviousness-type double patenting does not exist.

Claims 1-3, 5-7 and 13-15 of copending U.S. Patent Appln. No. 11/127,544 are directed to pharmaceutical compositions that are formulated in a controlled release delivery system and that include a platelet reducing agent that reduces platelet number. Instant claims 50 and 53-60 are directed to a sustained release device that includes an agent that reduces platelet count in a subject, where the device is adapted for long-term release of the agent for at least 7 days; the agent is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function; and the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent.

The issue, then, is whether, assuming the instant application issues later, a grant of a patent with any of the instant claims would extend a right of exclusivity claimed in any of claims 1-3, 5-7 and 13-15 of copending U.S. Patent Appln. No. 11/127,544. As noted, the test is whether the later issuing claims embrace the earlier issuing claims, and if not, whether the earlier issuing claims include or suggest, based upon the principles of claim interpretation, what is claimed in the later issuing case

In this instance, the instant claims, if related at all to claims 1-3, 5-7 and 13-15 of copending U.S. Patent Appln. No. 11/127,544, are a genus that overlaps with the genus claims claimed in copending U.S. Patent Appln. No. 11/127,544 or are a subgenus of the claims in the copending application. In either instance, the instant claims do not embrace the claims in the copending application.

As noted, the instant claims do not embrace the genus recited in the copending application. Furthermore, the claims in the copending application do not recite nor suggest, based upon any principles of claim interpretation, devices adapted for long-term release of the agent. The claims in the co-pending application are directed to pharmaceutical compositions formulated in a controlled release delivery systems; there is no recitation in the claims in the co-pending application of a device adapted for long-term release of the agent, as

instantly claimed. Hence, the instant claims, if issued after the claims in the copending application, would not extend a right of exclusivity granted in any patent granted on that application. Therefore, as between the instant claims and the claims in the co-pending application, obviousness-type double patenting does not exist.

REJECTION OF CLAIMS 50-53 AND 55-61 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 50-53 and 55-61 are rejected under 35 U.S.C. 112, second paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner alleges that the specification only provides a written description for certain species of the genus of agents that reduce platelet counts, such as those described on page 18 of the specification. The Examiner contends that there is insufficient written description that would allow an artisan to recognize that the Applicant had possession of a composition that includes any species of the entire genus of agents that reduce platelet count as of the time of filing the original application.

Applicant respectfully traverses the rejection.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention

defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987).

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species that are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

THE CLAIMS

Claim 50 is directed to a sustained release device that includes an agent that reduces platelet count in a subject, where the device is adapted for long-term release of the agent for at least 7 days, the agent is released in an amount effective to reduce platelet count in a subject to at least a low normal level and the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent. Claims 52 and 55-61 depend from claim 50 and are directed to various embodiments thereof.

ANALYSIS

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not recognize in the applicant's disclosure a description of the invention defined by the claims. The Examiner states that the specification discloses species of the claimed genus on page 18, but alleges that such a disclosure is not sufficient to provide written description for the entire genus.

Applicant respectfully disagrees. The MPEP provides guidelines for a written description analysis of claims directed to a genus. For example, see MPEP2163(II)(A)(3)(a), which states:

> Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied.

A. The Claimed Genus

As discussed above, claim 50 is directed to a sustained release device that includes an agent that reduces platelet count in a subject, where the device is adapted for long-term release of the agent for at least 7 days, the agent is released in an amount effective to reduce platelet count in a subject to at least a low normal level and the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent. Thus, the "agent that reduces platelet count in a subject" represents a genus that encompasses the exemplified species and other species that are similar in function to the exemplified species. Applicant respectfully submits that the instant claims are not directed to any specific agent that reduces platelet count in a patient, but are directed to a sustained release device that releases the agent in an amount effective to reduce platelet count in a subject to at least a low normal level, the agent is not an MPL pathway inhibitory agent and the agent is leased for at least 7 days. Therefore any agent that reduces platelet count in a subject that is not an MPL pathway inhibitory agent is contemplated for use in the claimed device.

B. Variation Within the Genus

The specification teaches that common elements are shared among agents that reduce platelet count in a subject. For example, such agents have the specific effect of reducing only platelet count without affecting levels of other cell types, although the agent also may reduce levels of other cell types provided these latter reductions do not induce unacceptable levels of adverse side effects associated with such reduction in other cell types (*e.g.*, see page 17, line 7 through page 18, line 2). The specification teaches that agents that reduce platelet count in a subject include agents that reduce levels of megakaryocytes, the precursors of platelets; agents cytotoxic for a megakaryocyte lineage restricted cell, such as a platelet; and agents

that inhibit megakaryocyte function (*e.g.*, see page 18, lines 2-10). The specification further teaches that agents that reduce platelet count include those which, while not exclusive for the megakaryocyte lineage, have limited specificity for other cell lineages (*e.g.*, see page 19, lines 26-28). Thus, in light of the teachings of the specification and known in the art, those skilled in the art would recognize common functional features shared by agents that reduce platelet count in a subject.

C. Level of Skill in the Art

The level of skill in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the requirement is minimal.

D. Representative Number of Species

An adequate written description for a claimed genus need only provide "relevant, identifying characteristics" of a representative number of species (MPEP §2163). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure. The specification provides a representative number of species explicitly and implicitly. For example, the disclosure on page 18 recites:

> Agents already known to reduce platelet count include but are not limited to (1) cAMP phosphodiesterase inhibitors (e.g., anagrelide), 6,7-dichloro-1,5-dihydroimidazo-[2,1-b]quinazolin-2(3H)-one or 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-b]quinazolin-2-one (U.S. Pat. Nos. 3,932,407; 4,146,718; RE31,617, Haematologica 1992 77:40-3), (2) antibodies to cell surface receptors specifically expressed by platelets or megakaryocytes such as glycoprotein IIb/IIIa receptor antibodies, (3) most chemotherapeutic anti-cancer drugs such as busulphan (Br. J. Haematol. 1986 62:229-37), hydroxyurea (N Engl J Med 1995 332:1132-6), hepsulfan, phosphorus-32 (Br J Radiol 1997 70:1169-73), pipobroman (Scand J. Haematol 1986 37:306-9), cyclophosphamide (J Cell Physiol 1982 112:222-8), certain alkylating agents and certain antimetabolites, (4) cytokines, growth factors and interleukins such as alpha-interferon (Cancer Immunol Immunother 1987 25:266-73), gamma-interferon, transforming growth factor-beta, neutrophil activating peptide-2 and its analogs (U.S. Pat. No. 5,472,944), macrophage inflammatory protein and its analogs (U.S. Pat. No. 5,306,709), (5) compounds secreted by either platelets or megakaryocytes such as platelet-factor 4 (U.S. Pat. No. 5,185,323), transforming growth factor-beta, the 12-17 kD glycoprotein produced by megakaryocytes, thrombin and thrombo-spondin and its amino (1-174 amino acid) terminal fragment (J Lab Clin Med

1997 129:231-8), and (6) other agents including anti-cheloid agents such as Tranilast (Rizaben) (J Dermatol 1998 25:706-9); forskolin and spleen anti-maturation factor (U.S. Pat. No. 4,088,753).

Each of the cited references is incorporated by reference in the application. Thus, the specification provides specific exemplary agents that reduce platelet count. These include, *e.g.*, anagrelide, 6,7-dichloro-1,5-dihydroimidazo-[2,1-*b*]-quinazolin-2(3H)-one, 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one, glycoprotein IIb/IIIa receptor antibodies, busulphan, hydroxyurea, hepsulfan, phosphorus-32, pipobroman, cyclophosphamide, alpha-interferon, gamma-interferon, transforming growth factor-beta, neutrophil activating peptide-2 and its analogs, macrophage inflammatory protein and its analogs, platelet-factor 4, transforming growth factor-beta, the 12-17 kD glycoprotein produced by megakaryocytes, thrombin and thrombospondin and its amino (1-174 amino acid) terminal fragment, Tranilast (Rizaben), forskolin and spleen anti-maturation factor. Hence, the specification explicitly discloses several exemplary platelet reducing agents by family (cAMP phosphodiesterase inhibitors, antibodies to cell surface receptors specifically expressed by platelets or megakaryocytes, chemotherapeutic anti-cancer drugs, cytokines, growth factors, interleukins, compounds secreted by either platelets or megakaryocytes, anti-cheloid agents and inhibitors of platelet CAMP20 phosphodiesterases) and provides more than one representative species for each exemplary family of platelet reducing agents.

Applicant respectfully submits that the specification teaches *in vitro* and *in vivo* assays for testing putatively useful agents. For example, the specification describes *in vitro* assays that examine the morphology, number and/or colony forming ability of platelets or platelet precursor cells after exposure to an agent that reduces platelet count (*e.g.*, see page 20, line 31 through page 21, line 23). The specification also describes *in vivo* assays that include platelet count and bleeding assays (*e.g.*, see page 21, line 24 through page 22, line 16). The specification also directs those skilled in the art to assays routinely practiced by those of ordinary skill in the art, such as those described in *Harrison's Principles of Internal Medicine*, Isselbacher, McGraw Hill, New York (1994) (*e.g.*, see page 22, lines 14-16).

Thus, the specification clearly describes and identifies various agents that reduce platelet count, provides a list of exemplary agents that reduce platelet count and directs the skilled artisan to several references describing exemplary agents that reduce platelet count. The specification provides a written description for functional characteristics of the various agents that reduce platelet count and thus provides relevant, identifying characteristics for the

species of the genus. The specification exemplifies *in vitro* and *in vivo* methods for assaying for agents that reduce platelet count, including methods known to those skilled in this art. Hence, in this instance, there is no basis to conclude that a person skilled in the art at the time the original application was filed would not recognize in the applicant's disclosure a description of the invention defined by the claims. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed at the time of filing of the original application.

REJECTION OF CLAIMS 52 AND 54-56 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 52 and 54-56 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Claim 52 is rejected because the Examiner alleges that the recitation "agent for treating vascular disease" lacks antecedent basis. Claim 54 is rejected because the Examiner alleges that the recitation "a derivative of anagrelide" is indefinite and alleges that the skilled artisan would not be certain what constitutes a derivative of anagrelide and thus would not understand the metes and bounds of the claim. Claims 55 and 56 are rejected because the Examiner alleges that the stated amounts of agent are likely to be lethal doses.

Applicant respectfully traverses the bases for the rejection in turn below.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

ANALYSIS

Claim 52

The Examiner alleges that the that the recitation "agent for treating vascular disease" lacks antecedent basis. Claim 52 is amended herein to depend from claim 51. Claim 51 provides antecedent basis for the recitation "agent for treating vascular disease." Applicant respectfully submits that the amendment of claim 52 herein obviates the rejection.

Claim 54

The Examiner alleges that the skilled artisan would not understand what constitutes a "derivative of anagrelide." Applicant respectfully disagrees. Anagrelide is the generic name for the compound having the IUPAC name 6,7-dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3H)-one. The specification discloses that anagrelide derivatives are anagrelide analogs and teaches that an exemplary anagrelide derivative is 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-one. The specification also directs the skilled artisan to a number of patents and scientific articles that describe the synthesis of anagrelide derivatives using chemical modification methods routinely used in the art. For example, see page 19, lines 9-22 of the specification, which recites:

> A preferred agent is anagrelide. Although anagrelide is capable of affecting platelet function, it is used in the compositions and methods of the invention in a dose, formulation and administration schedule which reduces platelet count (preferably to below normal levels) without significantly impacting upon platelet function. Analogs *(e.g.*, derivatives) of anagrelide which are as effective or more effective than the parent compound are also intended for use in the method of the invention. Preferably, such analogs would also be screened for an increased potency and specificity towards the megakaryocyte lineage with limited side effects. Synthesis of anagrelide analogs can be accomplished through routine chemical modification methods such as those routinely practiced in the art. Analogs of anagrelide have been reported by a number of groups. Jones *et al.* reported the synthesis of an analog, RS-82856 (J. Med. Chem. 1987 30:295-303). Other inhibitors of platelet CAMP20 phosphodiesterases synthesized by directed replacement of side chains on anagrelide have been reported by Meanwell *et al.* (J. Med. Chem. 1992 35:2672-87). Other anagrelide analogs have been documented in U.S. Patents 3,932,407; 4,416,718 and RE 31,617.

Each of Jones *et al.*, Meanwell *et al.* and U.S. Patents 3,932,407; 4,416,718 and RE 31,617 are incorporated by reference in the application (*e.g.*, see page 38, lines 1-2). Meanwell *et al.* (J. Med. Chem. 1992 35:2672-87, referenced in the specification and previously provided in an Information Disclosure Statement) describes a series of 1,3-dihydro-2H-imidazo[4,5-*b*]-quinolin-2-one derivatives, substituted at the 7-position with functionalized side chains and other structural modifications that include variation of the side-chain terminus, side-chain length and side-chain connecting atom. Meanwell *et al.* describes anagrelide derivatives that incorporate at the side-chain terminus functional moieties, including carboxylic acid, ester, amide, alcohol, acetate, nitrile, tetrazole, and phenyl sulfone moieties. Beverung, Jr. *et al.* describes optionally substituted 1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-ones and 6-[H]-1,2,3,4-tetrahydropyrimido-[2,1-*b*]-quinazolin-2-ones as anagrelide derivatives, including 7-bromo-1,2,3,5-tetrahydro-imidazo-[2,1-*b*]-quinazolin-2-one, 7-nitro-1,2,3,5-tetrahydro-

imidazo[2,1-*b*]-quinazolin-2-one, 7-amino-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-one, 6-hydroxy-1,2,3,5-tetrahydro-imidazo[2,1-*b*]-quinazolin-2-one, 7-hydroxy-1,2,3,5-tetrahydro-imidazo[2,1-*b*]-quinazolin-2-one, 8-bromo-6-[H]-1,2,3,4-tetrahydropyrimido[2,1-*b*]-quinazolin-2-one, 6-methyl-7-nitro-1,2,3,5-tetrahydro-imidazo[2,1-*b*]quinazolin-2-one, 7-bromo-6-methyl-1,2,3,5-tetrahydro-imidazo[2,1-*b*]-quinazolin-2-one, 7-chloro-6-methyl-1,2,3,5-tetra-hydroimidazo[2,1-*b*]-quinazolin-2-one, 6-chloro-7-bromo-1,2,3,5-tetrahydro-imidazo[2,1-*b*]-quinazolin-2-one, 6,7-dichloro-1,2,3,5-tetra-hydroimidazo[2,1-*b*]quinazolin-2-one, 7-amino-6-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-one, 6,7-dihydroxy-1,2,3,5-tetrahydro-imidazo[2,1-*b*]quinazolin-2-one, 6-methyl-1,2,3,5-tetrahydroimidazo-[2,1-*b*]quinazolin-2-one, 3-(carbethoxymethyl)-3,4-dihydro-5-methyl-4-methylene-1-*H*-quinazolin-2-one, 3-(carbethoxy-methyl)-4,5-dimethyl-1,2,3,4-tetrahydroquinazolin-2-one, 2-chloro-3-carbethoxy-methyl-4,5-dimethyl-3,4-dihydro-quinazoline, 5,6-dimethyl-1,2,3,5-tetrahydro-imidazo[2,1-*b*]quinazolin-2-one, 3-(carbethoxy-methyl)-3,4-dihydro-6-methyl-4-methylene-1-*H*-quinazolin-2-one, 3-(carbethoxymethyl)-4,6-dimethyl-1,2,3,4-tetrahydroquinazolin-2-one, 2-chloro-3-carbethoxy-methyl-4,6-dimethyl-3,4-dihydroquinazoline, 5,7-dimethyl-1,2,3,5-tetrahydroimidazo-[2,1-*b*]-quinazolin-2-one, 5-methyl-3-(carbethoxymethyl)-1,2,3,4-tetra-hydroquinazolin-2-one, 2-chloro-3-carbethoxy-methyl-5-methyl-3,4-dihydroquinazoline hydrochloride and 6-methyl-1,2,3,5-tetrahydro-imidazo-[2,1-*b*]quinazolin-2-one (U.S. Pat. No. 3,932,407). Jenks *et al.* describes alkyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrohalides, including 6,7-dichloro-1,5-dihydroimidazo[2,1-*b*]-quinazolin-2(3H)-one hydrochloride, ethyl 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydrobromide, ethyl 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydrobromide, 6,7-dichloro-1,5-dihydro-imidazo[2,1-*b*]-quinazolin-2(3H)-one monohydro-chloride monohydrate, methyl 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydrobromide, *n*-propyl 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydro-bromide, isopropyl 5,6-dichloro-3,4-dihydro-2(1H)-iminoquinazoline-3-acetate hydrobromide, *n*-butyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrobromide, methyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrochloride, *n*-propyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrochloride, isopropyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrochloride, *n*-butyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydrochloride, methyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydroiodide, *n*-propyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydroiodide, isopropyl 5,6-dichloro-3,4-dihydro-2(1H)-

iminoquinazoline-3-acetate hydroiodide and *n*-butyl 5,6-dichloro-3,4-dihydro-2(1H)-imino-quinazoline-3-acetate hydroiodide (U.S. Pat. No. 4,146,718). Jones *et al.* describes the anagrelide derivative N-cyclohexyl-N-methyl-4-(7-oxy-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-one) butyramide (J. Med. Chem. 30: 295-303 (1987)). Venuti *et al.* describes structural variations of N-cyclohexyl-N-methyl-4-[(1,2,3,5-tetrahydro- 2-oxoimidazo[2,1-*b*]-quinazolin-7-yl)-oxy]butyramide, including 7-(*N*-imidazolyl)-1,2,3,5-tetrahydro-2-oxo-imidazo[2,1-*b*]-quinazoline, 7-[ω-(*N*-imidazolyl)propyloxy]-1,2,3,5-tetrahydro-2-oxo-imidazo[2,1-*b*]-quinazoline, 7-[ω-(*N*-imidazolyl)hexyloxy]-1,2,3,5-tetrahydro-2-oxo-imidazo[2,1-*b*]-quinazoline (J. Med. Chem. 31: 2136-2145 (1988)). Thus, the specification describes what is intended by the recitation "derivative of anagrelide."

Applicant also respectfully submits that derivatives of anagrelide are known in the art. Chodnekar *et al.* (U.S. Pat. No. 4,256,748) describes a series of tetrahydroimidazo[2,1-*b*]-quinazolin-2-ones. Jones *et al.* (U.S. Pat. No. 4,490,371) describes another series of tetrahydroimidazo[2,1-*b*]quinazolin-2-one derivatives useful as thrombogenic agents. Hewawasam *et al.* (U.S. Pat. Nos. 5,348,960 and 5,208,237) describe a series of 1,3-dihydro-2H-imidazo[4,5-*b*]quinolin-2-ones.

Thus, Applicant respectfully submits that one of skill in the art, in light of what is known in the art and the teachings of the specification, would understand what is meant by the recitation "a derivative of anagrelide" and would be able to determine the metes and bounds of the claims. Thus, the term "a derivative of anagrelide" is not incompletely defined.

Claims 55 and 56

Claims 55 and 56 are rejected because the claims recite "g/kg/day," which results in a large amount of agent. This appears to be an error introduced in the Preliminary Amendment. A typographical error omitted the "μ" from the amount of agent in the listing of claims filed with the Preliminary Amendment. As originally filed, claims 55 and 56 recite μg/kg/day. As amended herein, claims 55 and 56 recite μg/kg/day. Hence, the rejection is obviated by the amendment of claims 55 and 56 herein.

THE REJECTION OF CLAIMS 50-53 AND 55-61 UNDER 35 U.S.C. §103(a)

Claims 50-53 and 55-61 are rejected under 35 U.S.C. §103(a) over Lindahl (U.S. Patent No. 6,083,518) because Lindahl allegedly teaches every element of the claims except the length of time the agent is released. The Examiner urges that it would have been obvious to a person of ordinary skill in the art to have made a composition that includes busulfan that is released over any amount of time and at any rate. With respect to claim 51, the Examiner

urges that an ordinarily skilled artisan would be motivated to include aspirin in the device in order to decrease the pain of a subject, and alleges that aspirin qualifies as an agent for treating vascular disease. This rejection is respectfully traversed.

RELEVANT LAW

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

In addition, if the proposed modification of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

THE CLAIMS

Claim 50 is directed to a sustained release device that includes an agent that reduces platelet count in a subject, where the device is adapted for long-term release of the agent for at least 7 days; the agent is released at a rate and in an amount effective to reduce platelet

count in a subject to at least a low normal level but without significantly affecting platelet function; and the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent. Claims 51, 52 and 55-61 ultimately depend from claim 50 and are directed to various embodiments thereof. For example, claim 51 specifies that the sustained release device of claim 50 further includes an agent for treating a vascular disease or complication.

TEACHINGS OF THE CITED ART - Lindahl (US 6,083,518)

Lindahl teaches sustained release formulations that include an active ingredient in a "glass-forming carrier" that is exemplified by polyethylene glycol (col. 3, lines 7-17). In one embodiment, the active agent is busulfan. Lindahl teaches that the release profile of an active agent from its formulation is controlled by means of the proportions of ingredients present in the composition (col. 2, lines 62-67). Lindahl teaches varying the combination of the glass-forming substance and placticizer such that proper glass transition temperature, consistency, and viscosity of its formulations for proper for administration and release of the active compound in order to have the desired profile (col. 6, lines 29-52). Lindahl teaches that by varying the composition, the release time profile and the release amount profile of the active agent can be controlled to achieve a controlled or sustained release (col. 7, lines 19-29). Lindahl teaches that an active agent is dissolved and not dispersed in a solid solution, which allows for enhanced solubility and solubility rate of an active agent (col. 2, lines 35-42).

Lindahl does not teach or suggest sustained release of an agent for at least seven days where the agent is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. Lindahl is silent regarding rate and dosage and does not suggest anything regarding effects on platelet function.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

(1) There would have been no motivation to have modified the teachings of Lindahl

The cited reference must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that applicant has done that would produce the claimed product (see, *e.g.*, *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). Lindahl teaches pharmaceutical compositions that include an active agent dissolved in a glass-forming carrier and a plasticizer. Lindahl provides no teaching or guidance regarding the period of time over which the active agent can

be released. Lindahl provides no teaching nor suggestion for inclusion of busulfan in a sustained release device adapted for long-term release for at least 7 days at a rate and dosage such that platelet count is reduced without substantially affecting platelet function. Busulfan is a chemotherapeutic agent administered to destroy bone marrow, which would destroy platelet function. There is no suggestion in Lindahl for selecting a rate and dosage that would not substantially affect platelet function.

Hence Lindahl provides no motivation for modifying its compositions that that would result in a sustained release device adapted for long-term release for at least 7 days at a dosage and rate that would lower platelet count without substantially altering platelet function. Furthermore, none of the art of record provides such motivation. For example, Van de Pette *et al.* (British J Haematology 62: 229-237 (1986)) teaches using busulfan to treat patients having primary thrombocythaemia, where the busulfan was administered daily (see page 230, second full paragraph). Thus, neither Lindahl nor the art of record provides any motivation to one of ordinary skill in the art to modify the formulations of Lindahl to result in a sustained release device adapted for long-term release of an agent for at least 7 days and rate that would lower platelet count without substantially altering platelet function.

With respect to the rejection as applied to claims 51 and 52, it is respectfully submitted that no evidence is provided to support the Examiner's position that "aspirin qualifies as an agent for treating vascular disease." The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970).

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. *In re Malcolm*, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

If this position is maintained, the Examiner must provide a reference supporting this position.

Notwithstanding this, Applicant respectfully submits that aspirin is known to interact with coadministered drugs (see, *e.g.*, Miners, "Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid," *Clin Pharmacokinet* 17(5): 327-44 (1989). Aspirin also is known to have serious side effects, including increasing the incidence of gastrointestinal bleeding and hemorrhagic strokes, which involve bleeding in the brain (*Research Activities* 257

(2002), "U.S. Preventative Services Task Force urges clinicians and patients to discuss aspirin therapy"). Among the side effects of busulfan is an increased risk of bleeding, and, at the time of filing the instant application and before, those of ordinary skill in the art recognized that aspirin should be avoided when using busulfan (*e.g.*, see "Busulfan," University of Maryland Medical Center, available on-line at http://www.umm.edu/altmed/ConsDrugs/Busulfancd.html, copyright 1978-2001; "Busulfan injection," Bassett Healthcare, last updated January 27, 2002, available on-line at http://www.bassett.org/pharmacy/drugInfo/selectedDrug.aspx?drug=78&pid=1015; "Myleran," Express Scripts, last updated July 2, 2003, available on-line at http://www.drugdigest.org/DD/DVH/Uses/0,3915,90%7CMyleran,00.html). Thus, in light of the teachings in the prior art that serious side effects of aspirin and busulfan include an increased risk of bleeding, and the specific teaching in the art that aspirin should be avoided when taking busulfan, Applicant respectfully submits that the prior art provides no motivation to an ordinarily skilled artisan to combine busulfan with aspirin to treat pain, as alleged by the Examiner.

Hence, one of ordinary skill in the art would not have been motivated in view of Lindahl to produce a sustained release device adapted to release an agent of interest for at least 7 days at a dosage and rate that would lower platelet count without substantially altering platelet function. There is no suggestion to vary the composition taught by Lindahl, and the reference contains no teaching or suggestion that such modifications are desirable.

(2) Notwithstanding the lack of motivation, modification of the teachings of Lindahl does not result in the instantly claimed delivery devices.

Applicant respectfully submits that modifying Lindahl as suggested by the Examiner does not result in the claimed delivery devices. Modifying the compositions of Lindahl to deliver an active agent for 7 days does not result in every element of the claimed delivery device. For example, Lindahl does not teach or suggest a sustained released device where the agent is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level without significantly affecting platelet function. The Examiner alleges that one of ordinary skill in the art would know how long the treatment should last and also would know the appropriate dosing regime effective to treat a subject who needs to be treated with busulfan. Applicant respectively disagrees.

a. Subject who needs to be treated with busulfan

Lindahl provides no teaching or suggestion regarding a subject who needs to be treated with busulfan. The extent of the teachings of Lindahl regarding busulfan is that it is a psycho-

pharmaceutical drug (col. 5, lines 16-17). Applicant respectfully submits that there is no teaching or suggestion in Lindahl that a dosing regime effective to treat a subject who needs to be treated with busulfan would be effective to reduce platelet count in a subject to at least a low normal level without significantly affecting platelet function.

b. Reducing platelet count in a subject to at least a low normal level

Applicant respectfully submits that whether optimization of a parameter is the result of obvious experimentation depends on what the prior art discloses with respect to the parameter in question, and whether any such experimentation comes from the teachings in the art. *See In re Sebek*, 465 F.2d 904, 906-07, 175 USPQ 93, 95 (CCPA 1972); *In re Waymouth*, 499 F.2d 1273,1276, 182 USPQ 290, 292 (CCPA 1974). In order for the claimed optimization to be the result of obvious experimentation, any such experimentation must come from within the teachings of the cited art, and the cited art must be viewed without reading into that art the teachings of the applicant (*In re Waymouth*, 499 F.2d 1273, 1276, 182 USPQ 290 (CCPA 1974).

Lindahl does not teach nor suggest that any of its disclosed biologically active agents can be selected and delivered in an amount effective to reduce platelet count in a subject to at least a low normal level without significantly affecting platelet function. Lindahl provides no teaching or suggestion of a rate of release of any of its exemplary bioactive compounds. Lindahl provides no teaching or suggestion of a duration of release of any of its exemplary bioactive compounds. Lindahl provides no teaching or suggestion that busulfan is an agent that can be delivered in an amount effective to reduce platelet count in a subject to at least a low normal level without significantly affecting platelet function. Neither Lindahl nor that which is known in the art provides any motivation to one of ordinary skill in the art to prepare a sustained release device that delivers busulfan in an amount that reduces platelet count in a subject to at least a low normal level. Lindahl provides no teaching regarding platelet counts. The prior art, such as Van de Pette *et al.*, teaches discontinuing busulfan administration when platelet count falls to less than $400x10^9$/L ($400x10^3$/μL) (see page 230, second full paragraph). The instant specification teaches (*e.g.*, at page 10, lines 24-25) that the typical range for platelets in a "healthy" human subject is about $150x10^3$ to $450x10^3$ platelets per μL of blood (mean $300x10^3$ platelets per μL). Hence, Van de Pette *et al.* teaches discontinuing busulfan administration to a patient with primary thrombocythaemia when a platelet count in the high end of the normal range is achieved. The instant specification teaches that subjects, including those with normal levels of circulating platelets, can derive medical benefit from a reduction in

platelet count to low or below normal levels without serious adverse consequences as a result of the platelet count reduction. For example, the specification recites (page 2, lines 4-18) that:

> The invention in a broad aspect involves the surprising discovery that subjects, including those with normal levels of circulating platelets, can unexpectedly derive medical benefit from a reduction in platelet count to below normal levels, without serious adverse consequences as a result of the platelet count reduction. The benefit may be proportional or correlative to the reduction in platelet count in a broad safety range. Thus in situations where it is desirable to inhibit a pathological condition or process mediated in part by normal levels of circulating platelets, subjects can be treated to lower platelet count preferably to a below normal level, thereby inhibiting the development, progression or propagation of the condition or accelerating or enhancing its regression. The methods of the invention are also useful for reducing the incidence of abnormal vessel growth induced by the presence of platelets.
> A method is provided for treating a subject to reduce the risk of developing an adverse is condition or to inhibit the progression and consequences of an adverse condition mediated at least in part by platelets. In some aspects, the subject is treated to reduce platelet count to low normal levels, while in other aspects the subject is treated to reduce platelet count to below normal levels.

Thus, any experimentation by the Applicant would not have come from within the teachings of the art, and the instantly claimed element that the agent is released in an amount effective to reduce platelet count in a subject to at least a low normal level without significantly affecting platelet function is therefore not the result of obvious experimentation.

It is respectfully submitted that the Office Action does not set forth a case of *prima facie* obviousness. The Examiner has not shown that the reference teaches or suggests to the person of ordinary skill in the art to make the changes that would produce the claimed subject matter, nor that such modification would result in all the elements of the claimed subject matter.

THE REJECTION OF CLAIMS 50-61 UNDER 35 U.S.C. §103(a)

Claims 50-61 are rejected under 35 U.S.C. §103(a) over Fleming *et al.* (U.S. Patent No. 4,432,980) because Fleming *et al.* allegedly teaches every element of the claims except sustained release compositions, but the Examiner alleges it would be obvious to a person of ordinary skill in the art to make a composition that could release agents over long period of times. The Examiner also alleges that an ordinarily skilled artisan would find it obvious to use the appropriate dosing to treat the condition of interest. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 50 is directed to a sustained release device that includes an agent that reduces platelet count in a subject, where the device is adapted for long-term release of the agent for at least 7 days; the agent is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function; and the agent is not a myeloproliferative leukemic (MPL) pathway inhibitory agent. Claims 51-61 ultimately depend from claim 50 and are directed to various embodiments thereof.

Added claim 63 is directed to a sustained release device that includes a device adapted for long-term delivery of an agent and an agent that reduces platelet count in a subject, where the agent is anagrelide or a derivative of anagrelide and the device is adapted for long-term release of the agent for at least 7 days, whereby the anagrelide is released at a rate and dosage that reduces platelet count without significantly affecting platelet function.

TEACHINGS OF THE CITED ART - Fleming *et al.* (U.S. Patent No. 4,432,980)

Fleming *et al.* teaches methods and compositions for inhibiting blood platelet aggregation, which reflects a change in platelet function. Fleming *et al.* teaches oral pharmaceutical compositions that include anagrelide and a non-steroidal anti-inflammatory agent capable of inhibiting blood platelet cyclo-oxygenase, and that such compositions provide an enhanced (supra-additive) inhibitory activity on blood platelet aggregation (col. 2, lines 31-41). Fleming *et al.* teaches the supra-additive effect occurs within a synergistic weight ratio range of anti-inflammatory agent to anagrelide (col. 4, lines 26-54). The compositions are formulated to be administered up to twice a day and preferably formulated for once-daily administration (col. 4, lines 64-66).

Thus, Flemming *et al.* teaches compositions for altering platelet function. Flemming *et al.* does not teach or suggest administering anagrelide or any agent at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. The compositions of Flemming *et al.* are formulated for adminstration at a dosage to alter platelet function.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

(1) There would have been no motivation to have modified the teachings of Fleming *et al.*

Fleming *et al.* teaches compositions containing a synergistic weight ratio range of anti-inflammatory agent to anagrelide formulated for administration up to twice a day. Fleming *et al.* does not teach or suggest a sustained release device for long-term delivery of an agent. Fleming *et al.* provides no motivation to the ordinarily skilled artisan to modify its pharmaceutical composition that would result in a sustained release device that is adapted for long-term release of the agent for at least 7 days in which the agent is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. No art of record provides such motivation. The prior art teaches short-term use of anagrelide. For example, Andes *et al.* (Thromb Haemostas (Stuttgart) 52(3): 325-328 (1984)) teaches that anagrelide is best limited to short-term use because of is reduction of platelet count. Andes *et al.* teaches that "although the fall in the observed platelet counts was modest when it occurred, this would probably preclude the long-term use of anagrelide" (see page 328, left column, first paragraph). Andes *et al.* teaches administering anagrelide in 0.5mg or 1mg tablets by mouth twice daily (page 325, right column, last paragraph). Accordingly, the prior art teaches formulations for daily administration as single dosage and that anagrelide is to be used only for short term applications. Therefore, there would have been no motivation to have modified the teachings of Fleming *et al.* to modify its pharmaceutical composition that would result in a sustained release delivery device that is adapted for long-term release of anagrelide for at least 7 days and where anagrelide is released at a rate and in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. None of the cited art suggests sustained release and none suggest a titration of the dosage to achieve a reduction in platelet count without a substantial alteration in platelet function. In Fleming *et al.* and other references of record, anagrelide is administered to alter platelet function.

(2) Notwithstanding the lack of motivation, modification of the teachings of Fleming *et al.* does not result in the instantly claimed delivery devices.

Claims 50-61

Fleming *et al.* does not teach or suggest other elements of the claimed sustained release devices. The sustained release devices of claims 50-61 include as an element that the agent is released in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. Fleming *et al.* teaches

compositions that include a combination of anagrelide with a non-steroidal anti-inflammatory agent, where the combination has supra-additive blood platelet anti-aggregation activity.

Platelets play a major role in the blood-clotting process and platelet aggregation is a measure of platelet function (Flores, "Platelet Aggregation Test," Gale Encyclopedia of Medicine, 2002). Thus, compositions with anti-aggregation activity affect platelet function. Antagonists of platelet function are used to prevent thrombosis and to alter atherosclerotic vascular disease (*Goodman & Gilmans's The Pharmacological Basis of Therapeutics*, (9th ed., Hardman *et al.*, eds., 1996, page 1353). The compositions of Fleming *et al.* include a combination of anagrelide and a non-steroidal anti-inflammatory agent within a synergistic weight ratio range that provides an enhanced (supra-additive) inhibitory activity on blood platelet aggregation (col. 2, lines 31-41). Thus, the compositions of Fleming *et al.* significantly affect platelet function. The instant claims are directed to sustained release devices that release an agent in an amount effective to reduce platelet count in a subject to at least a low normal level, where the agent is released in an amount that does not significantly affect platelet function. Fleming *et al.* provides no motivation to the ordinarily skilled artisan to modify its pharmaceutical composition so that it does not inhibit platelet aggregation. Such a modification of Fleming *et al.* would change the principle of operation of the composition of Fleming *et al.* The composition of Fleming *et al.* is designed to inhibit platelet function, specifically platelet aggregation, while the instant sustained release device releases the agent at a rate and in an amount that reduces platelet count in a subject to at least a low normal level but does not significantly affect platelet function. Thus, the pharmaceutical composition of Fleming *et al.* and the instantly claimed sustained release device are mutually exclusive. Thus, Fleming *et al.* does not provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that applicant has done that would produce the claimed sustained release device.

There is no teaching in Fleming *et al.* directed to reducing platelet count, nor any teaching or suggestion to reduce platelet count to at least a low normal level. Fleming *et al.* does not teach or suggest an amount of anagrelide that reduces platelet count in a subject to at least a low normal level. Fleming *et al.* does not teach or suggest any experimentation for achieving reduced platelet count in a subject to at least a low normal level. There is no appreciation that reduction of platelet count to at least low normal levels is beneficial, even in normal subjects, especially for inhibiting vaso-occlusive events in such subjects. The prior art does not teach or suggest the therapeutic and prophylactic benefit of reducing platelet counts to at least low normal levels.

Hence, the compositions of Fleming *et al.* have an anti-aggregation affect on platelets and thus significantly affect platelet function. Fleming *et al.* does not teach or suggest any release rate or release amount of anagrelide that is affective to reduce platelet count in a subject to at least a low normal level. Thus, even if, arguendo, the compositon of Fleming *et al.* was modified to result in a device adapted to deliver the combination for at least 7 days, this does not result in every element of claim 50. Applicant respectfully submits that claims 51-61 ultimately depend from claim 50 and therefore include the limitations thereof. Therefore, Fleming *et al.* does not teach or suggest every element of the subject matter of claims 50-61.

It is respectfully submitted that the Office Action does not set forth a case of *prima facie* obviousness. The Examiner has not shown that the reference teaches or suggests to the person of ordinary skill in the art to make the changes that would produce the claimed subject matter, nor that such modification would result in all the elements of the claimed subject matter. Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Claim 63

Fleming *et al.* does not teach or suggest the sustained release device of claim 63. Claim 63 includes as an element that the agent is released in an amount effective to reduce platelet count in a subject to at least a low normal level but without significantly affecting platelet function. As discussed above, Fleming *et al.* does not teach or suggest a device adapted for long-term release of anagrelide for at least 7 days, where the anagrelide is released at a rate and dosage that reduces platelet count without significantly impacting platelet function.

Claim 65

With respect to claim 65, it specifies that the device contains anagrelide or a derivative of anagrelide as the only active agent. Fleming *et al.* teaches oral pharmaceutical compositions that include anagrelide in combination with a non-steroidal anti-inflammatory agent capable of inhibiting blood platelet cyclo-oxygenase, and that such compositions provide an enhanced (supra-additive) inhibitory activity on blood platelet aggregation. Fleming *et al.* teaches that the supra-additive effect of its combination of anagrelide with a non-steroidal anti-inflammatory agent allows the dosage of anagrelide that would normally be required for achievement of a certain level of anti-aggregation activity to be reduced to a level that is otherwise minimally effective for inhibiting platelet aggregation (col. 5, lines 34-

40). Thus, one of ordinary skill in the art would not have been motivated to modify the compositions of Fleming *et al.* by removing the non-steroidal anti-inflammatory agent, since Fleming *et al.* teaches that the amount of anagrelide used in its compositions is minimally effective for inhibiting platelet aggregation. Thus, removing the non-steroidal anti-inflammatory agent from the compositions of Fleming *et al.* would render them useless for their intended purpose, namely inhibiting platelet aggregation, and change the principle of operation of the compositions of Fleming *et al.* Therefore, the reference does not teach or suggest to the person of ordinary skill in the art to make the changes that would produce the sustained release device of claim 63, nor that such modification would result in all the elements of the claimed subject matter.

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In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

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